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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,196	12/04/2001	Keith D. Allen	R-632	6896

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EXAMINER	
BERTOGLIO, VALERIE E	

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,196	ALLEN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-2, 11-13, 24-28, and 33-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *3-10,14-23 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Election/Restrictions

Applicant's election with traverse of Invention III, claims 6,7,9 and 14-21 in paper No. 8, dated 12/04/2002 is acknowledged. Applicant's arguments are found partially persuasive and Inventions II, III and IV will be rejoined and Inventions IX and X will be rejoined.

The traversal is partially on the ground(s) that a search of Invention I claims and Invention II-VI or Invention VII claims together would not be an undue burden because a reasonable search would produce results related to the targeting construct of Invention I and the cells of Invention II or the animals of Invention III or the methods of screening using the transgenic animal of Invention IV, or the methods of screening using the transgenic cells of Invention V, or the compounds of Invention VI and VII. This argument is not found persuasive because it is maintained that each of the inventions of Invention I and Invention II-VI or VII require a separate search status on the basis of each of Inventions II-VII requiring a materially different product from that of Invention I, which is separately classified. In particular, Invention I is directed to methods of making a gene targeting construct that is <u>not</u> necessary to disrupt FPR-RS4 in cells or in animals. Materially different constructs can be used to disrupt FPR-RS4. Furthermore, the nucleic acid sequences of Invention I and the cells of Invention II or the animals of Invention III are structurally and functionally different. As such, Invention I and Invention II or Invention III require materially different reagents and technical considerations such that a proper search for both inventions would require an extensive search for materially different methods thereby placing an undue search burden upon the Examiner.

Furthermore, the nucleic acid of Invention I and the compounds of Invention VI or VII are structurally and functionally distinct. The nucleic acid is not required for the compounds and the compounds are not necessary for the nucleic acid. Therefore, it is maintained that the Invention I and Invention II-VI or VII are distinct due to distinct structures, classification and method steps and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of Invention I-VII or IX claims and Invention VIII claims together would not be an undue burden. The examiner maintains that Invention I-VII or IX and Invention VIII are patentably distinct because Inventions I-VII or IX do not require the phenotypic database and the database does not require Inventions I-VII or IX. The reagents used in and the products of Invention I-VII or IX are functionally and structurally distinct from the database of Invention VIII and each has a different purpose. Furthermore, the burden required to search Inventions I-VII or IX with the phenotypic electronic database, which has a different classification, would be undue.

The traversal is partially on the ground(s) that a search of Inventions I-VII and the method of treating anxiety using FPR-RS4 of Invention IX together would not be an undue burden. The examiner maintains that Invention I-VI or VII and Invention IX are patentably distinct because the nucleic acid construct of Invention I, the cells of Invention II, the transgenic animal of Invention III, the methods of using a transgenic animal of Invention IV, the methods of using cells of Invention V, or the modulating agents of Invention VI or VII do not require the methods of treatment of Invention IX and

the methods treatment do not require any of Inventions II-VII. The nucleic acid construct, the cells, the animal and the modulators have distinct and different purposes from the method of treating anxiety using FPR-RS4. Furthermore, the burden required to search the products or reagents used in each of Inventions I-VI or VII with method of treating anxiety, which has a different classification, would be undue.

The traversal is partially on the ground(s) that a search Invention I-VI or VII and the pharmaceutical composition of Invention X together would not be an undue burden. The examiner maintains that Invention I-VI or VII and Invention X are patentably distinct because the nucleic acid construct of Invention I, the cells of Invention II, the transgenic animal of Invention III, the methods of using a transgenic animal of Invention IV, the methods of using cells of Invention V, or the FPR-RS4 modulators of Invention VI or VII do not require the pharmaceutical of Invention X and the pharmaceutical does not require any of Inventions I-VII. The nucleic acid construct, the cells, the animal and the modulators have distinct and different purposes from the pharmaceutical. Furthermore, the burden required to search the Inventions I-VI or VII with the pharmaceutical of Invention X, which has a different classification, would be undue.

The traversal is partially on the ground(s) that the applicants disagrees "with the examiner's assertion that the claims of Invention II and V are unrelated" and adds further that a search of Inventions II and V together would not be an undue burden. The examiner does not assert that the inventions are unrelated but that the inventions are patentably distinct because Inventions II and V are related as product and process of use wherein the process for using the product as claimed can be practiced with another

materially different product and further, the product as claimed can be used in a materially different process of using that product (see MPEP §806.05(h)). Furthermore, burden is not the only parameter used as the basis for restriction.

The traversal is partially on the ground(s) that a search of the cells of Invention II or the transgenic animals of Invention III and the compounds of Invention VI or VII together would not be an undue burden. The examiner maintains that Invention II or III and Invention VI or VII are patentably distinct because the cells or animals are structurally and functionally distinct from the compounds. The cells or animals can be used for in vitro assays, to study function of FPR-RS4, to produce proteins, or to test gene expression while the compounds can be used to modulate gene expression. The cells or animals each have a distinct and different purpose from the compounds. Furthermore, the burden required to search the cells or animals with the compounds, which have a different classification, would be undue.

The traversal is partially on the ground(s) that a search of the transgenic animal of Invention III and the method of using cells to identify an agent (Invention V) together would not be an undue burden and that the inventions are not patentably distinct. The examiner maintains that the inventions are structurally and functionally distinct, have different purpose and use, and are classified differently. Therefore, inventions III and V are patentably distinct and the burden required to search Invention III with Invention V would be undue.

The traversal is partially on the ground(s) that a search of the methods of using a transgenic animal or cells Invention IV or V and the compounds of Invention VI or VII

together would not be an undue burden. The examiner maintains that the methods of using a transgenic animal or cells and the compounds of Invention VI or VII are patentably distinct because the animals and cells are structurally and functionally distinct from the compounds. Neither the animals nor the cells are necessary for the compounds, nor are the compounds necessary for the methods of using the animals or cells. Furthermore, the burden required to search the methods of using the animals or cells with the compounds, which have a different classification, would be undue.

With exception of arguments directly pertaining to Inventions II, III and IV, which have been rejoined or to Inventions IX and X which have been rejoined, the restriction requirement is still deemed proper and is therefore made **FINAL.**

Claims 1-34 are pending, however, claims 1-2,11-13, 24-28, and 33-34 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 8. Claims 3-10,14-23, and 29-32 are under current examination.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequence in Figure 2A requires a SEQ ID NO.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing

into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Specification

The disclosure is objected to because of the following informalities:

The sentence bridging lines 19-21 on page 1 is incomplete.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-10,14-23, 29-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3-10,14-23, 29-32 encompass more than one FPR-RS4 gene as they are drawn to "an FPR-RS4 gene". The claims encompass any FPR-RS4 gene that may exist in each and every species of animal. The specification teaches only one, mouse FPR-RS4 gene (SEQ ID NO: 1; page 3, line 18) and does not disclose that other FPR-

RS4 genes exist or have the same function as the FPR-RS4 gene disclosed. Therefore, adequate written description to support the claims encompassing more than the one, disclosed FPR-RS4 gene is lacking.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the FPR-RS4 gene encompassed by SEQ ID NO:1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 3-10,14-23, 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse or mouse cell whose genome comprises a homozygous disruption in the FPR-RS4 gene wherein said mouse exhibits increased anxiety, or deficits in motor coordination, balance, ataxia or decreased susceptibility to seizure, does not reasonably provide enablement for any

transgenic non-human animal or a cell of any species with a disruption of any FPR-RS4 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 3-5,8 and 22 are directed to a cell comprising a disruption in an FPR-RSS4 gene. Claim 6 is directed to a non-human transgenic animal with a disruption in an FPR-RS4 gene. Claims 7,9,14-21, are directed to a transgenic mouse with a disruption in an FPR-RS4 gene, wherein the transgenic mouse exhibits increased anxiety (claim 15 and 16), or deficits in motor coordination, balance, or ataxia (claims 17-19) or decreased susceptibility to seizure (claims 20 and 21). Claims 10, 23, and 29-32 are directed to methods of using a transgenic mouse with a disruption in an FPR-RS4 gene to screen for modulators of FPR-RS4 function or expression (claim 10) or to evaluate treatments for phenotypes associated with an FPR-RS4 deficiency (23 and 29-32).

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene which were intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Moens (1993, Development, Vol. 119, pages 485-499) taught two mutations produced by homologous recombination in

two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (page 486, column 1, first full paragraph). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) teaches that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, the phenotype of knockout mice was unpredictable.

The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Thus, the combination of elements (protein, promoter, species of protein, and species of transgenic) required to obtain a desired effect were not within the realm of routine experimentation at the time of filing.

Not only is the difference in transgenic mice and rats unpredictable for reasons stated above, the art at the time of filing was such that a number of significant limitations regarding the production of non-human transgenic animals existed. Wall (1996, Theriogenology, Vol. 45, pages 57-68) disclosed the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic non-human mammal of interest.

The art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, embryonic stem cell technology must be available to carry out the method. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute

to the germ line in any species other than mouse (page 65). Furthermore, other potential methods of generating transgenic embryos using homologous recombination had not been developed at the time the invention was made (McGreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages 928-929; Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). Thus, at the time of filing, knockout animals could not be prepared for any species other than mouse.

1) The specification does not provide adequate guidance for one of skill in the art to generate non-human transgenic animals having a disruption in the FPR-RS4 gene (claim 6) in any species other than mouse. The methods of gene targeting such as employed in the instant invention require embryonic stem cells. The guidance offered in the specification is limited to the production of knockout mice using mouse ES cells and no teachings or guidance are offered in regard to how one would have prepared any other species of animal using targeted mutagenesis. The specification discloses injecting cells comprising a disruption in the FPR-RS4 gene into a blastocyst to generate transgenic animals (page 17, lines 4-6). However, the specification and the art at the time of filing fail to disclose any ES cells other than mouse ES cells that contribute to the germline. Without such guidance, it would require undue experimentation for one of skill in the art at the time of filing to make any transgenic, non-human animal with a disruption in the FPR-RS4 gene.

2) Applicants fail to enable the making and/or using a transgenic having a phenotype other than increased anxiety, or deficits in motor coordination, balance, ataxia or decreased susceptibility to seizure. The specification does not provide an

enabled use for the knockout claimed that has a wild type phenotype, which is encompassed by claims 6,7,14. As set forth in the art, the phenotype of a transgenic animal was unpredictable at the time of filing. The specification does not overcome the unpredictability inherent in generating knockout mice such that any phenotype could be obtained other than increased anxiety, or deficits in motor coordination, balance, ataxia or decreased susceptibility to seizure in FPR-RS4 knockout mice. Without such guidance, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to obtain any phenotype other than increased anxiety, or deficits in motor coordination, balance, ataxia or decreased susceptibility to seizure.

3) The specification teaches that only mice homozygous for a disruption in FPR-RS4 displayed increased anxiety, or deficits in motor coordination, balance, ataxia or decreased susceptibility (page 56, lines 7-10; page 57, lines 7-9; page 57, lines 23-24). The specification did not disclose a phenotype for mice heterozygous for an FPR-RS4 disruption. Therefore, the claims should be limited to a homozygous disruption of the FPR-RS4 gene.

4) The specification fails to enable disrupting any FPR-RS4 gene in a mouse or any other species or a cell other than a mouse cell. The specification only teaches one FPR-RS4 gene (SEQ ID NO: 1; page 3, line 18). The specification does not provide adequate guidance for determining other FPR-RS4 genes or that other FPR-RS4 genes exist or have the same function as the FPR-RS4 gene disclosed. Limiting claims 3-6

and 10 to a transgenic mouse or mouse cell and deleting "a" preceding "FPR-RS4" in claims 3,4,6,9,10,14,15,17,20,23, would overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 3-9, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Gao (1998, Genomics, Vol. 51, pages 270-276).

Capecchi taught transforming a cell with a nucleic acid construct comprising a disruption in the HoxA-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous HoxA-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the FPR-RS4 gene.

However, at the time the claimed invention was made, Gao taught the cloning of the mouse FPR-RS4 gene (entire document and for further sequence detail GenBank Accession No. AF071182).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Capecchi wherein the gene was FPR-RS4 as taught by Gao. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the FPR-RS4 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the FPR-RS4 gene to determine its role in relation to other FPR genes, as described by Gao (1998, Genomics, Vol. 51, pages 270-276).

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

2) Claims 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beach (*1999, USPN 5,919,997*) in view of Gao (1998, Genomics, Vol. 51, pages 270-276).

Beach taught transforming a cell with a nucleic acid construct comprising a disruption in the INK4 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous INK4 locus, and using said cell to generate a knockout

mouse whose genome comprises a disruption in the INK4 gene (column 14, lines 61-66). Beach taught administering compounds to the transgenic knockout mice comprising a disruption in the INK4 gene to screen for agents that affect the INK4 mutant phenotype and modulate the expression or function of INK4 (column 26, lines 51-54 and claim 11). Beach differs from the claimed invention in that the targeting construct does not disrupt the FPR-RS4 gene.

However, at the time the claimed invention was made, Gao taught the cloning of the mouse FPR-RS4 gene (entire document and for further sequence detail GenBank Accession No. AF071182).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Beach wherein the gene was FPR-RS4 as taught by Gao and to use said animals to screen for compounds that modulate FPR-RS4 expression or function by assessing changes in the FPR-RS4 mutant phenotype. One of ordinary skill in the art would have been sufficiently motivated to replace the INK4 gene with the FPR-RS4 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse and to use the mouse to screen for agents that affects or ameliorates a mutant phenotype. One of ordinary skill in the art would have been sufficiently motivated to disrupt the FPR-RS4 gene to determine its role in relation to other genes in the FPR gene cluster, as described by Gao or to screen for modulators of FPR-RS4 expression or function as taught by Beach.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner

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